IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NATURAL ALTERNATIVES INTERNATIONAL, INC., *et al.*,	)	
Plaintiffs,	)	C.A. No. 09-626-GMS
v.	)	**JURY TRIAL DEMANDED**
VITAL PHARMACEUTICALS, INC., *et al.*	)	
Defendants.	)	
VITAL PHARMACEUTICALS, INC.,	)	
Counterclaim/Third-Party Plaintiff,	)	
v.	)	
NATURAL ALTERNATIVES INTERNATIONAL, INC., and COMPOUND SOLUTIONS, INC.,	)	
Counterclaim/Third-Party Defendant.	)	

PLAINTIFFS' OPENING BRIEF IN SUPPORT OF CLAIM CONSTRUCTION

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CASES

Plaintiff, Natural Alternatives International Inc. ("NAII") respectfully submits this Memorandum supporting its Proposed Claim Construction of U.S. Patent Nos. 5,965,596 ("the '596 patent"), 6,172,098 ("the '098 patent") and 6,426,361 ("the '361 patent") (collectively "the patents-in-suit").

INTRODUCTION

The invention of the '596, '098 and '361 patents relates to the use of the amino acid β-alanine as a dietary supplement that can increase the anaerobic working capacity of muscles, *i.e.*, dietary supplements containing the amino acid β-alanine help athletes train, or perform for longer periods of time without feeling tired. The dietary supplements can contain other amino acids, or compounds that enhance muscular performance, such as creatine. Prior to the pioneering work of the inventors of the patents-in-suit[1], dietary supplements available to counteract the onset of fatigue from prolonged exercise were of limited value. The research of the inventors demonstrated that these earlier dietary supplements were inefficient and did not lead to the increased muscular performance provided by beta-alanine.

While performing research on the physiology of muscles and how muscles work, Drs. Roger Harris and Mark Dunnett discovered that a particular dipeptide, beta-alanylhistidine,[2] was particularly useful to counteract fatigue, and its concentration in muscles could be increased by providing the amino-acid beta-alanine (also represented as β-alanine). β-alanine and the amino acid L-histidine are covalently joined by an enzyme to form β-alanylhistidine. While β-alanine is a naturally occurring amino acid, it is not one of the 20 common amino acids found in proteins. It differs from the common amino acid L-alpha-alanine as set forth on the next page.

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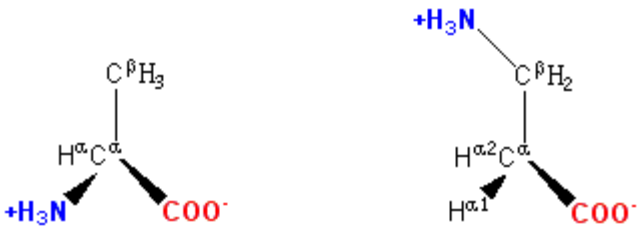
[1] *See, e.g.*, Harris, RC et al. (2006). "The absorption of orally supplied β-alanine and its effect on muscle carnosine synthesis in human vastus lateralis." *Amino Acids* 30 (3): 279–289.

[2] Beta-alanylhistidine is also represented as β-alanylhistidine. Beta-alanylhistidine is also known as carnosine. *See, e.g.*, JX. 3 at col. 2, ll. 1-4.



L-α-alanine **β-alanine**

See, e.g., Wikipedia description of β-alanine, *available at*, http://en.wikipedia.org/wiki/Beta-Alanine. Dipeptides, tripeptides, oligopeptides and polypeptides all contain more than one amino acid. In a dipeptide, tripeptide, oligopeptide, or polypeptide, a portion of the individual amino acid is removed and the remaining residue is linked together covalently. A single amino acid or mono peptide can exist as an ester, amide or a salt.[3] Esters are chemical compounds created by reacting an acid with an alcohol. An amide of beta-alanine, can be created by reacting beta-alanine with an amine. The linkage would be between the nitrogen of the amine and the former carboxyl of the amino acid. The amino acid β-alanine can be made into salt by reacting it with sodium hydroxide or a similar base. In an aqueous solution, the salt will usually dissociate into individual ions, such as a beta-alanine ion and a sodium ion. β-alanylhistidine, therefore, is a dipeptide containing two amino acid residues that are joined via a peptide bond.[4]

Drs. Harris and Dunnett discovered that they could regulate hydronium ion concentrations in human muscle by providing β-alanine as a supplement. The β-alanine is quickly adsorbed from the digestive system and transported by the blood to the tissue. Importantly, increasing the amount of β-alanylhistidine in the muscle cells increases the cells

[3] Esters are chemical compounds created by reacting an acid with an alcohol. Amides are chemical compounds typically created by reacting an acid with an amine, which is a derivative of ammonia. Salts are chemical compounds created by reacting an acid and a base.

[4] A peptide bond is formed by joining one end of one amino acid to the other end of another amino acid by removing elements from both of the amino acids. *See, e.g.*, definition of peptide bond, *available at*, http://dictionary.reference.com/browse/peptide+bond.

ability to function with insufficient amounts of oxygen, *i.e.*, anaerobic conditions, thereby limiting muscle fatigue and soreness. Thus, in providing a supplement of β-alanine to the diet, an athlete could avoid muscle fatigue and soreness.

The claim interpretation issues here are straightforward as they rely on the intrinsic evidence and follow well-settled precedent from the Supreme Court and the Court of Appeals for the Federal Circuit. Faced with what should therefore be a focused and simple task, defendants Vital Pharmaceuticals Inc. and DNP International Co., Inc. (collectively, "defendants") twist and distort the terms to broaden claim scope, offering constructions which the inventors clearly and unmistakably disavowed during prosecution. Defendants also conjure up constructions that are not supported by the intrinsic evidence. Defendants proffer these constructions in the hope that the claims will be declared invalid, as that is the only way they can avoid infringement of the patents-in-suit. In that light, this Brief provides NAII's proposed definition for each disputed claim term and the support in the intrinsic evidence for that definition. NAII will address defendants' proposed constructions in its opposition brief.

BACKGROUND OF THE PROCEEDING

A. The Parties

Natural Alternatives International Inc.

NAII was established in 1980. NAII is the owner of the patents-in-suit. NAII scientifically designs and customizes nutritional products based on the unique needs of individual clients, testing new products and formulas prior to full-scale production. NAII produces pilot or sample runs of product formulation prototypes to ensure stability and/or efficacy, to determine ingredient interactions, and test customer acceptance of the final product. NAII also directs and participates in clinical research studies to establish consumer benefits and scientific efficacy.

NAII's success in the formulation, development, manufacturing and marketing of specialized products is predicated on its dedication to research and development, technology, science and state-of-the-art manufacturing. This research is supported by NAII's licensing activities and sales. The comprehensive service NAII offers has established NAII as an innovator in the field of nutritional science. As such, NAII recognized the importance of the research being conducted by the inventors of the patents-in-suit and collaborated with them at an early stage in the prosecution of the patents-in-suit, through an exclusive license agreement.

Vital Pharmaceuticals Inc.

VPX manufactures and sells a broad range of products, including dietary supplements containing β-alanine. VPX manufactures and sells several products that are used as dietary supplements and contain β-alanine. VPX provides instructions related to the use of these dietary supplements, including instructions related to the use and consumption of products containing β-alanine and creatine.

DNP International Co., Inc.

DNP supplies β-alanine to dietary supplement manufacturers, such as VPX. DNP markets and distributes β-alanine and provides information regarding the benefits of using β-alanine containing products.

B. The '596 Patent

The '596 patent issued on or about October 12, 1999, entitled "Methods and compositions for increasing the anaerobic working in tissues." JX. 1. The named inventors are Roger Harris and Mark Dunnett. JX. 1 at JA1. At issue in the '596 patent are claims 1-7 and 9-11, which read as follows (with disputed claim terms highlighted):

1. A method of regulating hydronium ion concentrations in a human tissue comprising: **providing an amount of beta-alanine to blood or blood plasma effective to increase beta-alanylhistidine dipeptide synthesis in the human tissue**; and exposing the tissue to the blood

or blood plasma, whereby the concentration of beta-alanylhistidine is increased in the human tissue.

2. The method of claim 1, further comprising **providing an amount of L-histidine to the blood or blood plasma effective to increase beta-alanylhistidine dipeptide synthesis in the human tissue**.

3. The method of claim 1, further comprising increasing a concentration of creatine in the human tissue.

4. The method of claim 3, further comprising **providing an amount of L-histidine to the blood or blood plasma effective to increase beta-alanylhistidine dipeptide synthesis in the human tissue**.

5. The method of claim 3, wherein increasing the amount of creatine in the human tissue includes providing an amount of creatine to the blood or blood plasma effective to increase the concentration of creatine in the human tissue.

6. The method of claim 5, further comprising **providing an amount of L-histidine to the blood or blood plasma effective to increase beta-alanylhistidine dipeptide synthesis in the human tissue**.

7. The method of claim 1, wherein the providing step includes ingestion of a composition including the amount of **beta-alanine**.

9. The method of claim 1, further comprising **increasing a concentration of insulin in the blood or blood plasma**.

10. The method of claim 9, further comprising **providing an amount of L-histidine to the blood or blood plasma effective to increase beta-alanylhistidine dipeptide synthesis in the human tissue**.

11. The method of claim 1, wherein the human tissue is a skeletal muscle.

C. The ‘098 Patent

The ‘098 patent issued on or about January 9, 2001, entitled “Methods and compositions for increasing the anaerobic working in tissues.” JX. 2. It is a Divisional patent of the ‘596 patent with the same inventors. JX. 2 at JA23. At issue in the ‘098 patent is claim 11[5], which reads as follows (with disputed claim terms highlighted):

11. A method of increasing the anaerobic working capacity of a human tissue comprising: **providing an amount of beta-alanine to blood or blood plasma effective to increase beta-alanylhistidine dipeptide synthesis in a human tissue; providing an amount of L-histidine to the blood or blood plasma effective to increase beta-alanylhistidine dipeptide synthesis**;

[5] Claim 11 depends from claim 5 and the language of claim 5 is included in the language set forth here in relation to claim 11.

and exposing the human tissue to the blood or blood plasma, whereby the concentration of beta-alanylhistidine is increased in the human tissue.

D. The '361 Patent

The '361 patent issued on or about July 30, 2002, entitled "Methods and compositions for increasing the anaerobic working capacity in tissues." JX. 3. It is a Continuation patent of the '098 patent. JX. 3 at JA49. The '596, '098 and '361 patents were all examined by the same Patent Examiner. Jx. 1 at JA1; JX. 2 at JA23; JX. 3 at JA49. At issue in the '361 patent are claims 5-7, 17-20, 32 and 33, which read as follows (with disputed claim terms highlighted):

5. A **dietary supplement** comprising a mixture of a creatine and a composition comprising an amino acid or an **active derivative** thereof selected from the group consisting of a **beta-alanine**, an ester of a **beta-alanine** and an amide of a **beta-alanine**.

6. The **dietary supplement** of claim 5 in a **unit dosage form**.

7. The **dietary supplement** of claim 6, wherein one dose comprises up to 99% by weight of **beta-alanine**.

17. A **dietary supplement** comprising a mixture of a carbohydrate and a composition comprising an amino acid or an **active derivative** thereof selected from the group consisting of a **beta-alanine**, an ester of a **beta-alanine** and an amide of a **beta-alanine**.

18. The **dietary supplement** of claim 17 in a **unit dosage form**.

19. The **dietary supplement** of claim 17, wherein one dose comprises up to 99% by weight of **beta-alanine**.

20. The **dietary supplement** of claim 17, wherein one dose comprises up to 99% by weight of a carbohydrate.

32. A human **dietary supplement** comprising **beta-alanine** and **L-histidine**.

33. A human **dietary supplement** comprising an amino acid or an **active derivative** thereof selected from the group consisting of a **beta-alanine**, an ester of a **beta-alanine** and an amide of a **beta-alanine** and **L-histidine**.

LAW OF CLAIM CONSTRUCTION

Claim construction is a matter of law. *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 384-391 (1996). If the meanings of the claim terms are in dispute, the court's interpretation of the scope and meaning of the claims is the first step towards determining issues of validity and infringement. *Id.* at 384. When interpreting terms in a claim, the court must first look to the

intrinsic evidence, which includes (1) the language of the claims; (2) the specification; and (3) the prosecution history. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995) (*en banc*), *aff'd*, 517 U.S. 370 (1996). Intrinsic evidence is the most significant source of information for determining the proper meaning of claim terms. *Guttman v. Kopykake Enterprises, Inc.*, 302 F.3d 1352, 1362 (Fed. Cir. 2002); *see also Phillips v. AWH Corp. et al.*, 415 F.3d 1303, 1312, 1315-17 (Fed. Cir. 2005) (*en banc*).

To define claim scope, a court initially looks to the words of the claims themselves. *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996); *see also Phillips*, 415 F.3d at 1312-13. The meaning of disputed terms must be determined by considering the surrounding words of the claims. *See Brookhill-Wilk 1, LLC v. Intuitive Surgical, Inc.*, 334 F.3d 1294, 1299 (Fed. Cir. 2003). "Proper claim construction, however, demands interpretation of the entire claim in context, not a single element in isolation." *Hockerson-Halberstadt, Inc. v. Converse Inc.*, 183 F.3d 1369, 1374 (Fed. Cir. 1999). Words in a claim are generally given their ordinary and customary meaning unless a patentee chooses to be his own lexicographer and provides a special definition of the term in the patent specification or prosecution history. *Kopykake*, 302 F.3d at 1359-60 ("the specification acts as a dictionary when it contains definitions of terms"); *Digital Biometrics v. Indentix, Inc.*, 149 F.3d 1335, 1344 (Fed. Cir. 1998); *Vitronics*, 90 F.3d at 1582.

When the specification provides more than one definition for a claim term, the court should avoid definitions upon which the Patent Office could not reasonably have relied when it issued the patent. *Genentech, Inc. v. Wellcome Foundation, Ltd.*, 29 F.3d 1555, 1563-64 (Fed. Cir. 1994). Definitions of claim terms contained in the specification can be modified by statements made during prosecution of the patent before the Patent Office. *Rheox, Inc. v. Entact,*

Inc., 276 F.3d 1319, 1327 (Fed. Cir. 2002) (stating that the court was not persuaded by arguments that the written description defined certain terms to include the disputed term because "[r]eading the written description alone, this argument might be effective, but in light of the prosecution history, which was generated after the written description was drafted, it is apparent that Rheox relinquished any coverage of the disputed term."); *see also, Spectrum Intern., Inc. v. Sterilite Corp.*, 164 F.3d 1372, 1379-80 (Fed. Cir. 1998) (determining that the arguments made by Spectrum during prosecution limited the claim scope despite what was in the written description). For this prosecution disclaimer to be valid, the prosecution history must show clear and unmistakable surrender of subject matter for a court to determine that a potential claim construction has been relinquished. *See, e.g., Eagle Comtronics, Inc. v. Arrow Communication Laboratories, Inc.*, 305 F.3d 1303, 1316 (Fed. Cir. 2002); *see also, Omega Eng'g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1325-26 (Fed. Cir. 2003); *Computer Docking Station Corp. v. Dell, Inc.*, 519 F.3d 1366, 1375 (Fed. Cir. 2008); *Abbott Laboratories v. Sandoz, Inc.*, 566 F.3d 1282, 1288-89 (Fed. Cir. 2009).

When more than one related patent is in dispute, a court interprets common claim terms consistently across an entire patent family. *NTP, Inc. v. Research in Motion, Ltd.*, 418 F.3d 1282, 1293 (Fed. Cir. 2005). Thus, a claim term that appears in both the parent specification and continuation patent specifications should be construed identically in each. *See e.g., Sanders Brine Shrimp Co. v. Bonneville Artemia Int'l, Inc.*, 970 F. Supp. 892 (D. Utah 1997); *Omega Eng'g, Inc.*, 334 F.3d at 1333 (holding that disclaimers made during the prosecution of a patent will attach to a CIP of the patent); *Ormco Corp. v. Align Technology, Inc.*, 498 F.3d 1307, 1315-16 (Fed. Cir. 2007) (holding that the claims were limited and did not include limitations found in

the prior art that the applicants had disclaimed during prosecution and that these statements in the prosecution history of the parent applied to the claims in the other patents-in-suit).

Whether to treat a preamble as a claim limitation is determined on the facts of each case in light of the claim as a whole and the invention described. *See Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002). "[W]hen reciting additional structure or steps underscored as important by the specification, the preamble may operate as a claim limitation." *Id.* "[T]he preamble is analyzed to ascertain whether it states a necessary and defining aspect of the invention, or is simply an introduction to the general field of the claim." *On Demand Mach. Corp. v. Ingram Indus.*, 442 F.3d 1331, 1343 (Fed. Cir. 2006). Even where the limitation does not appear in the body of the claims, the written description and statements made during prosecution can require a term in the preamble to limit a claim. *Computer Docking Station Corp.* 519 F.3d at 1375.

NAII'S CLAIM CONSTRUCTION

Pursuant to the Scheduling Order, the parties exchanged claim terms, met, and conferred to narrow the claim terms in dispute. The parties agreed that for terms not in dispute that the plain and ordinary meaning is sufficient, but if the Court determines that a dispute as to the plain and ordinary meaning of those terms arises at a later date, NAII respectfully requests the opportunity to propose a construction at that time. The parties have also agreed on the construction of the term "mixture." The terms that are still in dispute and that require construction are highlighted in the claims set forth, *supra*.

A. The terms β-alanine and L-Histidine in the asserted claims designate the individual amino acids

"beta-alanine" means "the individual amino acid, beta-alanine, or its salt, ester or amide"
"L-histidine" means "the individual amino acid, L-histidine, or its salt, ester, or amide"

The terms β-alanine and L-histidine in the patents-in-suit[6] must be construed to mean the individual amino acids, or a salt, ester, or amide of the individual amino acids. The terms cannot be construed to include β-alanine and/or L-histidine in a dipeptide such as carnosine. The written description of the patents-in-suit states:

> [e]ach of the beta-alanine or L-histidine can be the individual amino acids, or *components* of dipeptides, oligopeptides, or polypeptides. The beta-alanine or L-histidine can be active derivatives. An active derivative is a compound derived from, or a precursor of, the substance that performs in the same or similar way in the body as the substance, or which is processed into the substance and placed into the body. Examples include, for example, esters and amides

JX. 3 at col. 2, ll. 43-50 (emphasis added). The written description, therefore, provides multiple definitions for the β-alanine and L-histidine. This is like the term at issue in the *Genentech* case. There, the court determined that it should avoid those definitions upon which the Patent Office could not reasonably have relied when it issued the patent. *Genentech, Inc.*, 29 F.3d at 1563-64. Here, the Court should do the same.

During prosecution of the '596 patent, the applicants made arguments to distinguish their invention over the prior art. Specifically, the applicants stated, "[i]n contrast to the present invention, the compositions and methods described in Setra's invention teaches dipeptides. In the present invention, β-alanine and/or L-histidine are administered to regulate hydronium ion concentrations. Setra does not teach, suggest or mention using monopeptides for the treatment of hydronium ions." JX 4 at JA74. Setra was disclosed to the Examiner during prosecution of the patents-in-suit and describes the use of dipeptides, such as carnosine. JX 8; JX 9; JX 10; JX 11. This statement by applicants during prosecution was a clear and unmistakable disavowal that the applicants' invention encompassed dipeptides such as carnosine, that were disclosed and claimed

[6] All of the patents-in-suit have the same written description and claim priority back to a common ancestor and so citations to col. __ and ll. __ herein refer to the column and line numbers of the '361 patent, however, this same information is found in all the patents-in-suit.

in the Setra reference. *See Eagle Comtronics, Inc.*, 305 F.3d at 1316; *Omega Eng'g, Inc.*, 334 F.3d at 1325-26; *Computer Docking Station Corp.*, 519 F.3d at 1375; *Abbott Laboratories*, 566 F.3d at 1288-89.

To the extent the specification might be construed to have a contrary definition, this statement in the prosecution history overrules any such definition of the terms "β-alanine" or "L-histidine". The Federal Circuit has determined that despite any definition contained in the written description, a statement made during the prosecution history will modify, or limit the particular definition. *Rheox, Inc.*, 276 F.3d at 1327; *Spectrum Intern., Inc.*, 164 F.3d at 1379-80. An applicant will frequently narrow and add limitations to the claimed invention during prosecution. Thus, an applicant is not forced to proceed with the claims as filed but can amend the claims, either explicitly or through arguments and statements made during prosecution. It is clear that the statement made during prosecution modifies the definition of β-alanine and L-histidine in the specification to exclude dipeptides, such as carnosine, and specifically limits it to "monopeptides," or individual amino acids.

Furthermore, the written description of the patents-in-suit discloses the use of the individual amino acids β-alanine and L-histidine. *See, e.g.*, JX 3 at col. 6, ll. 56-64. ("During the supplementation period an identical feeding regime was implemented. However, each hard feed meal was supplemented with beta-alanine and L-histidine (free base). Beta-alanine and L-histidine were mixed directly into the normal feed. … Beta-alanine was administered at 100 milligrams per kilogram body weight and L-histidine at 12.5 milligrams per kilogram body weight."). This demonstrates that the β-alanine and L-histidine were added to the diet as individual amino acids ("free base") and that the amount of β-alanine added was approximately 8 times that of L-histidine. The written description highlights why this must be the case.

Specifically, the specification discloses that in a typical fed state the concentration of β-alanine is low compared to the concentration of L-histidine in blood, *i.e.*, the amount of β-alanine available from eating a normal diet containing dipeptides, such as carnosine, is low compared to L-histidine, and that the amount of β-alanine available is more important than the amount of L-histidine. JX 3 at col. 5, ll. 11-29. That is, the body is more sensitive to each additional amount of β-alanine than it is to an equal amount of L-histidine. Taking the claims as a whole, the entire written description, and the prosecution history, it is clear that the Examiner understood the terms β-alanine and L-histidine to mean the individual amino acids, their salts, esters or amides. Further it is clear that the Examiner did not consider β-alanine and L-histidine in the form of dipeptides, such as carnosine, encompassed by the claims, despite any confusion over the definition in the written description. This is because of the clear and unmistakable disavowal of this claim scope during prosecution of the '596 patent. The Court, therefore, should adopt the reasonable interpretation upon which the Patent Office relied when it issued the '596 patent. See *Genentech, Inc.*, 29 F.3d at 1563-64.

Additionally, because all of the patents-in-suit have identical disclosures and claim priority from a common ancestor, the terms β-alanine and L-histidine must be construed identically for all three patents. *See NTP, Inc., Ltd.*, 418 F.3d at 1293; *Omega Eng'g, Inc.*, 334 F.3d at 1333; *Ormco Corp.*, 498 F.3d at 1315-16. This is strengthened by the fact that the Examiner in all the cases was the same individual and that he made a restriction requirement in the first Office Action that he issued. JX 1; JX 2; JX 3; JX 6. Due to this restriction requirement, the Examiner understood that the statements made by the applicants during the prosecution of the '596 patent applied equally to the applications that ultimately issued from the original application as the '098 and '361 patents. The Court, therefore, should construe the terms

β-alanine and L-histidine consistently across all the patents-in-suit to mean "the individual amino acid, β-alanine, or its salt, ester or amide" or "the individual amino acid, L-histidine, or its salt, ester or amide".

B. The term dietary supplement cannot include a conventional food substance

"dietary supplement" means "an addition to the normal diet in a pill, capsule, tablet, powder, or liquid form, which is not a conventional food, and effectively increases the function of tissues when consumed"

The term "dietary supplement" appearing in the preamble of certain claims of the '361 patent excludes natural, or conventional food substances. *See, e.g., Catalina Mktg. Int'l, Inc.*, 289 F.3d at 808 ("[W]hen reciting additional structure or steps underscored as important by the specification, the preamble may operate as a claim limitation."); *On Demand Mach. Corp.*, 442 F.3d at 1343 ("In considering whether a preamble limits a claim, the preamble is analyzed to ascertain whether it states a necessary and defining aspect of the invention, or is simply an introduction to the general field of the claim."); *Computer Docking Station Corp.* 519 F.3d at 1375 (explaining that even where the limitation does not appear in the body of the claims, the written description and statements made during prosecution can require a term in the preamble to limit a claim). Here, the specification clearly underscores the importance of supplements and demonstrates that the term is a necessary and defining aspect of the invention.

Specifically, the patents-in-suit disclose the importance of supplements to compensate for the reduced levels of nutrients in the diet. The specification states:

> Natural food supplements are typically designed to compensate for reduced levels of nutrients in the modern human and animal diet. In particular, useful supplements increase the function of tissues when consumed. It can be particularly important to supplement the diets of particular classes of animals whose [] normal diet may be deficient in nutrients available only from meat and animal produce (e.g., human vegetarians and other animals consume an herbivorous diet).

JX. 3 at col.1, ll. 18-25. This demonstrates that the applicants intended that the supplements of the invention were something other than simply conventional food because they were intended to compensate for reduced levels of nutrients in the diet, *i.e.*, nutrients available from conventional foodstuffs and that this was important to the overall invention. Additionally, conventional foodstuffs, like meat and animal products, cannot be used to supplement the diets of particular humans that do not eat these conventional foodstuffs. For example, conventional foodstuffs like meat and animal products cannot be used to supplement the diets of vegetarians. This also shows that the applicants understood the importance of the form that the β-alanine and/or L-histidine take for the supplements of the invention to be useful.

The written description also underlines the importance that supplements of the invention be something other than a conventional food because conventional foods will not contain sufficient quantities of β-alanine and/or L-histidine. For example, the specification states, "[t]he compositions and methods can contribute to correcting the loss of beta-alanine, L-histidine, or creatine due to degradation or leaching of these constituents during cooking or processing. The compositions and methods can also contribute to correcting the absence of these components from a vegetarian diet." JX 3, col. 3, ll. 54-59. β-alanine only comes from animals and animal products; it is clear the inventors were not suggesting vegetarians become carnivores, but instead that they use a supplement that is not a conventional foodstuff in their diet. Moreover, the dietary supplements of the patents-in-suit cannot be conventional food because the processing of conventional food, for example by cooking, removes the β-alanine and/or L-histidine from the food. This shows that the dietary supplements of the invention are a necessary and defining aspect of the invention and should be construed. Furthermore, the written description of the patents-in-suit discloses that these dietary supplements cannot be conventional foodstuffs. *See*,

e.g., JX. 3 at col. 1, ll. 18-25; col. 3, ll. 54-59. The Court, therefore, should construe the term "dietary supplement" to mean "an addition to the normal diet in a pill, capsule, tablet, powder, or liquid form, which is not a conventional food, and effectively increases the function of tissues when consumed."

C. The term "Active Derivative" excludes dipeptides such as carnosine

"active derivative" means "a compound derived from, or a precursor of, the substance that performs in the same or similar way in the body as the substance, or which is processed into the substance and placed into the body, and excludes dipeptides, oligopeptides and polypeptides"

The term "active derivative" should be construed to exclude dipeptides, such as carnosine, because of the statements made by the applicants during prosecution and the claims and written description exclude such a construction. As discussed above, during the prosecution of the '596 patent, the applicants clearly and unmistakably disavowed any claim scope encompassing β-alanine contained in dipeptides, such as carnosine. Although this was in relation to the claim terms β-alanine and L-histidine, it applies equally here.

Additionally, the term "active derivative" is part of a larger element of the claim which is "a composition comprising an amino acid or an active derivative thereof selected from the group consisting of a beta-alanine, an ester of a beta-alanine and an amide of a beta-alanine." *See, e.g.*, JX 3 at claims 5, 17, 33. Because a claim term cannot be construed in isolation, but must be construed in the context of the surrounding words, "active derivative" cannot encompass a dipeptide such as carnosine. *Brookhill-Wilk 1, LLC*, 334 F.3d at 1299; *Hockerson-Halberstadt, Inc.*, 183 F.3d at 1374. The term "active derivative," therefore, is an active derivative of an amino acid. An amino acid is not a dipeptide, which by definition is two amino acid residues chemically bonded to one another via a peptide bond.

The specification defines "active derivative" as "a compound derived from, or a precursor of, the substance that performs in the same or similar way in the body as the substance,

or which is processed into the substance and placed into the body. Examples include, for examples, esters and amides." JX. 3, col. 2, ll. 46-49. Further, the specification describes β-alanine and L-histidine as precursors of dipeptides like carnosine, not the other way round. JX. 3, col. 5, ll. 11-15. Moreover, the dipeptides of β-alanine and L-histidine do not perform in the same or similar way in the body as the individual amino acids. For example, the patents-in-suit state that the β-alanylhistidine dipeptides help in the buffering capacity of the muscles during periods of sustained exercise, whereas amino acids do not. *See, e.g.*, JX. 3 at col. 2, ll. 1-23; col. 4, l. 66-col. 5, l. 10. Also, the β-alanylhistidine dipeptides must be synthesized inside the muscle cell from the precursor amino acids, β-alanine and L-histidine. JX. 3 at col. 5, ll. 11-29. The β-alanylhistidine dipeptides, therefore, do not fit within the meaning of an active derivative that is set forth in the patents in suit. Accordingly, the term "active derivative" should be construed to mean "a compound derived from, or a precursor of, the substance that performs in the same or similar way in the body as the substance, or which is processed into the substance and placed into the body, and excludes dipeptides, oligopeptides and polypeptides."

D. The method claims of the patents-in-suit do not encompass providing a dipeptide such as carnosine to increase the synthesis of the dipeptide in muscle

"providing an amount of [beta-alanine or L-histidine] to blood or blood plasma effective to increase beta-alanylhistidine dipeptide synthesis in a human tissue" means "supplying to a human an amount of [beta-alanine or L-histidine] by ingestion and therefore, causing an increase in [beta-alanine or L-histidine] in blood or blood plasma above normal concentrations found in a typical fed state, and thereby increasing the synthesis of beta-alanylhistidine dipeptide in the tissue"

Providing an amount of β-alanine or L-histidine effective to increase dipeptide synthesis in muscle does not include providing a β-alanylhistidine dipeptide by ingestion or infusion because of statements made during prosecution of the patents-in-suit and the disclosures contained in the written description. The term "providing an amount of [β-alanine or L-

histidine] to blood or blood plasma effective to increase beta-alanylhistidine dipeptide synthesis in a human tissue" was originally presented in the application that issued as the '596 patent. JX. 12 at JA129. As discussed above, the applicants distinguished their invention over the prior art by stating "[i]n contrast to the present invention, the compositions and methods described in Setra's invention teaches dipeptides. In the present invention, β-alanine and/or L-histidine are administered to regulate hydronium ion concentrations. Setra does not teach, suggest or mention using monopeptides for the treatment of hydronium ions." JX. 4 at JA74. The applicants, therefore, made a clear and unmistakable disavowal that the methods encompassed providing β-alanylhistidine dipeptides.

Additionally, the written description discloses that the dipeptides in the muscle are synthesized from the precursor amino acids and that in a typically fed state, the concentration of β-alanine is much lower than L-histidine. JX. 3 at col. 5, ll. 11-29. This means that in a normal diet containing dipeptides such as carnosine, that more L-histidine is present than β-alanine. Importantly, the written description discloses that the carnosine synthase enzyme has a greater affinity for L-histidine than for β-alanine and that the limiting step for β-alanylhistidine dipeptide synthesis is the concentration of β-alanine. *Id.* Thus, the enzyme that combines β-alanine and L-histidine to form carnosine prefers L-histidine over β-alanine: to overcome this preference, the enzyme must be supplied with more β-alanine than L-histidine. In a typically fed state the amount of β-alanine is much lower than L-histidine and is not high enough to increase dipeptide synthesis in a human tissue. The term in dispute has the phrase "effective to increase beta-alanylhistidine dipeptide synthesis in a human tissue." Accordingly, an amount of β-alanine, or L-histidine, "effective to increase beta-alanylhistidine dipeptide synthesis in a human tissue," must be different than that which is found in a typically fed state, such as when

consuming dipeptides like carnosine. In the case of β-alanine, this must be higher than the β-alanine available from dipeptides like carnosine because the enzyme that combines β-alanine and L-histidine to form carnosine prefers L-histidine.

Because of this lower concentration of β-alanine compared to L-histidine and the need for β-alanine to effectively increase β-alanylhistidine dipeptide synthesis, it is necessary to give more β-alanine than L-histidine. This is also disclosed in the written specification. Specifically, the written description states, "[d]uring the supplementation period an identical feeding regime was implemented. However, each hard feed meal was supplemented with beta-alanine and L-histidine (free base). Beta-alanine and L-histidine were mixed directly into the normal feed. Individual doses of beta-alanine and L-histidine were calculated according to body weight. Beta-alanine was administered at 100 milligrams per kilogram body weight and L-histidine at 12.5 milligrams per kilogram body weight." JX. 3 at col. 6, ll. 56-64. This demonstrates that to effectively increase β-alanylhistidine dipeptide synthesis, more β-alanine than L-histidine is required. Giving dipeptides of β-alanine and L-histidine, such as carnosine, does not provide this higher ratio because the β-alanylhistidine dipeptides contain equal amounts of β-alanine and L-histidine. The term "providing an amount of [beta-alanine or L-histidine] to blood or blood plasma effective to increase beta-alanylhistidine dipeptide synthesis in a human tissue," therefore, requires that the amount of β-alanine or L-histidine provided be different than that which is provided by ingestion, or infusion of dipeptides of β-alanine and L-histidine, and that the amount be higher than that which is found in a typically fed state. Accordingly, the term should be construed to mean "supplying to a human an amount of [β-alanine or L-histidine] by ingestion and therefore, causing an increase in [β-alanine or L-histidine] in blood or blood

plasma above normal concentrations found in a typical fed state, and thereby increasing the synthesis of beta-alanylhistidine dipeptide in the tissue"

E. A unit dosage form only requires that there be a serving size

"unit dosage form" means "doses of a certain serving size that can be taken all at once, or in multiple parts throughout the day"

The term "unit dosage form" does not require that a single dose is contained by itself in a single unit. The written description clearly discloses that the dietary supplements of the patents-in-suit can be taken in various dose sizes and that these doses can be taken all at once or throughout the day. JX. 3 at col. 3, ll. 45-49; col. 5, l. 56- col. 6, l. 9. For example, the dose of β-alanine can be between 0.4 to 16 grams of β-alanine per day for an 80 kg person, which can be taken all at once, or in multiple parts throughout the day. JX. 3 at col. 5, l. 56- col. 6, l. 9. Moreover, the dose sizes disclosed in the written description are not amenable to being contained by itself in a single unit and therefore, must be taken in multiple parts throughout the day. For example, the dose sizes can range from 10 grams to 800 grams. JX. 3 at col. 3, ll. 45-49. It is not feasible, therefore, that a dose size of 800 grams be contained by itself in a single unit. The density of β-alanine is 1.437 g/cm^3. *See*, *e.g.*, Wikipedia description of beta-alanine, *available at*, http://en.wikipedia.org/wiki/Beta-Alanine. For a dose of 800 grams of β-alanine to be contained in a single unit would require that it be a volume of 557 cm^3. In real terms, this is equivalent to a small book. A construction that would require a person to consume something the size of a small book all at once is absurd. A unit dosage form contained in a single unit is not disclosed anywhere in the specification. What is disclosed, however, is that the doses can vary in size and that the doses can be taken all at once, or in multiple parts throughout the day. Accordingly, the term "unit dosage form," should be construed to mean "doses of a certain serving size that can be taken all at once, or in multiple parts throughout the day."

F. Increasing the concentration of insulin can include ingestion or infusion of agents that stimulate insulin production.

"increasing a concentration of insulin in the blood or blood plasma" means "the concentration of insulin in the blood or blood plasma is increased by ingesting or infusing insulin, or agents that stimulate the production of insulin"

The term "increasing a concentration of insulin in the blood or blood plasma" can include infusing, or ingesting agents that stimulate the production of insulin. The written description clearly discloses that the concentrations of components in the blood can be increased by infusion or ingestion of agents that can cause an increase in the concentration and that the dietary supplements of the patents-in-suit can include insulin, or agents that stimulate the production of insulin. JX. 3 col. 3, ll. 42-45; col. 5, ll. 52-54. The term "increasing a concentration of insulin in the blood or blood plasma," therefore, should be construed to mean "the concentration of insulin in the blood or blood plasma is increased by ingesting or infusing insulin, or agents that stimulate the production of insulin."

CONCLUSION

For the aforementioned reasons, NAII respectfully asks this Court to construe the disputed claim terms as set forth in NAII's proposed construction in the Joint Claim Chart submitted by the parties.

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CERTIFICATE OF SERVICE

I, David E. Moore, hereby certify that on March 25, 2011, the attached document was electronically filed with the Clerk of the Court using CM/ECF which will send notification to the registered attorney(s) of record that the document has been filed and is available for viewing and downloading.

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